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Risk Factors for the Development of Pleural Empyema in Children

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Summary. Pediatric pleural empyema has increased substantially over the past 20 years and reasons for this rise remain not fully explained. We investigated potential risk factors for the development of empyema in children by examining a cohort of patients with community-acquired pneumonia. Demographic, clinical, and socioeconomic characteristics, use of Ibuprofen prior to presentation and selected potential epidemiological risk factors were analyzed. Data were collected from a prospective etiological study of radiologically confirmed pneumonia in hospitalized children aged ≤16 years. One hundred sixty children were enrolled; 56% were male and 69% aged <5 years. Empyema complication developed in 40 (25%) children. Children with empyema were more frequently prescribed Ibuprofen prior to admission to hospital than those without (82% vs. 46.2%; OR 1.94, 97.5% credible interval 0.80–3.18). Bacterial infection was strongly associated with the development of empyema (OR 3.34, 97.5% credible interval 1.70–5.14). In contrast age, sex, maternal age, parental smoking, level of socioeconomic status, nursery attendance, asthma, household characteristics (bedrooms and number of occupants) were not significantly different between groups. In conclusion, children with pneumonia who developed empyema had more often received Ibuprofen prior to hospitalization and confirmed bacterial infection. We suggest a population-based study involving both primary and secondary care settings would help to investigate the role of Ibuprofen use in modulating the course of disease in children with pneumonia. **Pediatr Pulmonol. 2015;50:721–726.**

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INTRODUCTION

The incidence of pediatric pleural empyema has increased substantially over the past 20 years in developed countries leading to considerable research focus on this infection.[1,2] Factors that might determine the progression from uncomplicated community-acquired pneumonia (CAP) to complicated pneumonia or empyema remain uncertain.[3] Previous retrospective studies have suggested that children with empyema were older, had been unwell longer and were likely to have received antibiotics or Ibuprofen before presentation to hospital.[4,5]

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A significant association has also been found with infection with varicella-zoster virus in the preceding month of illness.[5]

Historically pleural infection has been difficult to study because of lack of a suitable in vivo model.[6] Recent advances in this area are starting to elucidate potential pathophysiological mechanisms.[7] Wilkosz et al.[7] described evidence of early pleural invasion in murine models of pleural infection even in the absence of established pneumonia. Identifying putative epidemiological risk factors that may contribute to the development of empyema is important in establishing effective public health interventions to reduce disease burden. We therefore used a nested case-control analysis to explore possible risk factors into the etiology of empyema among hospitalized children with CAP.[8]

METHODS

Participants

A prospective etiological study of pneumonia was conducted from October 2009 to March 2011.[8] Eligible children were aged $\leq$16 years who were hospitalized with clinical and radiological features suggestive of pneumonia. Children were from the North East of England (excluding Cumbria) who presented or were transferred to the pediatric services at both the Newcastle Hospitals and South Tees Hospitals NHS Foundations Trusts. The former site includes the regional cardiothoracic center where empyema is managed. Informed written consent was obtained from parents and assent from older children. Ethical and Caldicott approvals were granted (Newcastle and North Tyneside Research Ethics Committee [No: 08/H0906/105], and Research Approval Board at South Tees Hospitals NHS Trust [No: 2008075]).

Exclusion criteria included clinical diagnosis of bronchiolitis, hospitalization in the preceding 3 weeks, or normal chest radiograph after formal reporting by a radiologist. In the UK, children are assessed by a General Practitioner in primary care or accident and emergency team and then referred to a hospital-based pediatrician if secondary care is required.

Laboratory and Radiological Procedures and Case Definition

Microbiological and virological testing informed the etiology of pneumonia.[8] Identified pathogens were categorized as viral, bacterial, or mixed viral–bacterial infections according to defined diagnostic criteria (Table 1).[8]

Chest radiographs were taken upon admission to hospital and first reported by local radiologists then reviewed by a second consultant cardiothoracic radiologist at the regional center. All involved reporters received the same training in pediatric radiology and were either pediatric radiologists or general radiologists who regularly report chest radiographs for children. Radiographic findings were categorized into lobar, patchy, or perihilar according to WHO criteria.[9]

Empyema was clinically diagnosed and this was coupled with evidence of loculated pleural fluid on chest radiograph and/or chest ultrasound scan. Only those cases that required invasive management (pleural drainage

TABLE 1— Laboratory Investigations and Diagnostic Criteria of Likely Causative Pathogens of Pneumonia

Sample	Pathogen/antigen	Tests	Interpretation
Serum	Respiratory viruses	Complement fixation	Acute titer $\geq$1/128 or fourfold rise between paired sera
	Atypical bacteria		
	Mycoplasma	IgM antibody	Positive
	Group A *Streptococcus*	Antistreptolysin *O* titer (IU/ml)	Acute twofold rise or fourfold rise between paired sera
Blood	Bacteria	Culture	Growth
	Streptococcus pneumoniae	Real-time PCR	Positive
Nasopharyngeal secretions/sputum	Respiratory viruses	Real-time PCR	Positive
Tracheobronchial secretions (collected via endotracheal tube or bronchoalveolar lavage)	Respiratory viruses	Real-time PCR	Positive
	Bacteria	Culture/real-time PCR	Growth/positive
Pleural fluids	Bacteria	Culture	Growth
	Pneumococcal antigen	ELISA[1]	Positive
	Streptococcus pneumoniae	Real-time PCR	Positive

[1]ELISA, enzyme-linked immunosorbent assay.

and/or decortication) were included in the empyema group. All empyema cases had grossly drained purulent pleural fluid irrespective of the microbiological result.

Epidemiological Data

Possible determinants of CAP were selected based on the previous literature.[5,10,11] Data were collected on demographic and socioeconomic characteristics, use of Ibuprofen prior to presentation, and selected risk factors such as asthma, parental smoking, and nursery attendance. Pneumococcal immunization history was obtained for each child from parents, and where available it was cross-checked with the child's parent held health records. If there was uncertainty about the immunization history, general practice surgeries were contacted and practice records of vaccines given checked.

Parental occupation information was incomplete, therefore socioeconomic status and the measure of deprivation were derived for each child based on the index of multiple deprivation (IMD) score for the parental postcode of residence [The English Index of Deprivation 2007, Office for National Statistics (ONS)].[12]

Statistical Analysis

Values for missing data from the covariates were estimated from the known data in order to prevent interpretation bias. An advantage of this methodology is the ability to account for missing covariate data. Rather than discarding the cases, missing data can be simulated either from the total known population, or using information from known covariates to estimate based upon other similar individuals.

Univariate analysis assessed the association between possible risk factors and the development of empyema, with the general model structure:

$$Y_i \sim \text{Bernoulli distribution}(P_i)$$

$$\text{logit}\,(P_i) < -\alpha + \beta \text{cov}_i$$

where Y_i is the binary output for whether individual i has empyema, P_i is the probability of empyema, α is the intercept term, β is the regression coefficient, and cov_i is the covariate value for individual i. The Bernoulli distribution is a discrete probability distribution, which takes value 1 with success probability P, and value 0 with failure probability q, equal to $q = 1 - P$.

Data were analyzed using the R2jags package[13] within the R statistical software.[14] JAGS is "Just Another Gibbs Sampler."[15] It is a program for Bayesian models using Markov Chain Monte Carlo (MCMC) methods. A 10,000 iteration "burn-in" was followed by a 50,000 iteration sample; with model convergence assessed using the Gelman–Rubin diagnostic.[16] A model was assumed to have converged if the Gelman–Rubin diagnostic was below 1.1.[17] All of our models comfortably satisfied this requirement. A covariate was considered significant if 97.5% of its posterior distribution lay either above or below zero. Multivariate analysis included those variables identified as significant in the univariate analysis, using the same tests for significance. Similar subgroup analysis was conducted among only those children with lobar pneumonia in order to investigate if the findings could be replicated. When testing whether the type of infection is significant predictor for the development of empyema, mixed bacterial–viral infections were excluded from the analysis to avoid potential bias to the findings.

RESULTS

A total of 225 children were initially enrolled; 65 were excluded (60 had a normal chest radiograph, 5 lived outside of the North East of England), leaving 160 eligible for inclusion. Of these, 56% were males and 69% aged <5 years. There were no deaths. Based on age criteria, pneumococcal vaccination uptake among 119 eligible children was 94% (89 had PCV7, 10 PCV13, and 13 received combinations of each; Table 2).

Lobar consolidation was reported in 61% of children, perihilar in (21%) and patchy changes (18%). Pleural fluid (including empyema) was noted in 68 (42.5%) children: 55 (80.9%) together with lobar changes, 10 (14.7%) with patchy and 3 (4.4%) with perihilar. Empyema occurred in 40 (25%) children; with 36 lobar, 3 patchy, and 1 perihilar changes. There were no significant differences in age ($P = 0.650$) and sex ($P = 0.091$) between children with empyema and those with pneumonia only.

The etiological characteristics of pneumonia and pneumococcal serotype distribution of this cohort have

TABLE 2— Number of Received Doses of the Pneumococcal Conjugate Vaccine (PCV)

	Pneumonia without empyema	Pneumonia with empyema
Received doses of PCV	n	n
PCV7	(n = 67)[1]	(n = 22)[2]
1 dose	11	2
2 doses	15	4
3 doses	41	16
PCV13	(n = 10)[2]	(n = 0)
1 dose	4	—
2 doses	5	—
3 doses	1	—
Both PCV7 and PCV13	(n = 10)	(n = 3)
1 dose of each	1	—
2 PCV7 + 1 PCV13 doses	9	2
1 PCV7 + 2 PCV13 doses	—	1

[1]Five children had partial schedule with one dose less for their age.
[2]One child had one dose less for age.

been presented previously.[8] A likely causative pathogen was established in 61% of children; 31% viral, 17.5% bacterial, and 12.5% mixed infections. Pneumococcal infections accounted for 17.4% of children tested (14/93 [15%] and 10/45 [22.2%] in those aged under and over 5 years, respectively). Among those 40 children who developed empyema the causative bacterial pathogen was identified in 75%; 20 (66.7%) *Streptococcus pneumoniae* [serotypes 1 (n = 7), 3 (n = 5), 19A (n = 4), 7A/F (n = 1), non-typeable (n = 2) and one serotype was not processed for typing], 7 (23.3%) group A *streptococcus*, 2 (6.7%) *Staphylococcus aureus*, and 1 (3.3%) *Streptococcus intermedius*. Pneumococcal infection was identified in four children with pneumonia only; one serotype 1, one non-typeable serotype, and two were not processed for typing.

Table 3 summarizes the univariate and multivariate analyses. Children with empyema were more frequently prescribed Ibuprofen prior to admission to hospital than those who did not develop empyema (82% vs. 46.2%) (OR 1.94, 97.5% credible interval 0.80–3.18) and bacterial infection was strongly associated with the development of empyema (OR 3.34, 97.5% credible interval 1.70–5.14). In contrast age, sex, maternal age, parental smoking, level of socioeconomic status, nursery attendance, asthma, household characteristics (bedrooms and number of occupants) were not significantly different between groups. These findings were consistent in the subgroup analysis of only children with lobar pneumonia. Additionally, among children with lobar changes only, empyema occurred more often in boys than girls compared to those with pneumonia only (OR 5.07, 97.5% credible interval 0.80–19.58).

DISCUSSION

The present study demonstrated that children with pneumonia who developed empyema had more often received Ibuprofen prior to hospitalization and were more likely to have suffered proven bacterial infection. These findings were replicated when analyses included only children with lobar chest radiographic changes and are of potential importance to public health policymakers for disease prevention at the community level.

Our findings are broadly consistent with previous data. Byington et al.[5] found in a retrospective study empyema was associated with older age >3 years, recent varicella infection, pneumococcal infection with serotype 1, longer febrile illness and likely to receive antibiotics, and Ibuprofen before hospitalization.[5] In England and Wales non-PCV7 serotypes are now associated with invasive pneumococcal disease[18] and an increase in pneumococcal serotype 19A is associated with complicated pneumonia with empyema.[19] Francois et al.[4] found that suppurative complications of pneumonia were associated with older age, longer illness duration and frequently received antibiotics, and Ibuprofen prior presentation to hospital. However, of these, only use Ibuprofen was significant.[4] Ibuprofen was also found to be significantly associated with the occurrence of necrotizing fasciitis particularly

TABLE 3— Analysis of Possible Risk Factors Associated With the Development of Empyema in Children With Pneumonia

	Pneumonia without empyema (n = 120)	Pneumonia with empyema (n = 40)		Univariate analysis	Multivariate analysis
Characteristics	N/total (%)	N/total (%)	Missing data, n	OR (97.5% credible interval)	OR (97.5% credible interval)
Male sex	62 (51.7)	28 (70)	0	2.41 (1.05–4.89)	0.89 (−0.26–2.06)
Age (years)[1]	2.3 (4.0 ± 4.02)	3.6 (5.6 ± 4.65)	0	1.09 (1.00–1.18)	−0.05 (−0.18–0.09)
Under five	87 (72.5)	24 (60)		—	—
Under two	53 (44)	8 (20)		—	—
Socioeconomic status (IMD score)[1]	28.5 (33.8 ± 23.34)	30.8 (32.1 ± 20.71)	0	1.00 (0.98–1.01)	—
Classification of infection (viral/bacterial)[2]	47 (39.2)/10 (8.3)	2 (5.0)/18 (45.0)	83	54.25 (6.74–233.00)	3.34 (1.70–5.14)
Nursery attendance for preschool age group	31/79 (39.2)	12/24 (50)	0	2.09 (0.83–4.50)	—
Asthma	10 (8.3)	2 (5)	0	0.66 (0.07–2.11)	—
Maternal age (years)[1]	32 (32.4 ± 6.96)	34 (33.5 ± 7.36)	12	1.02 (0.97–1.08)	—
Parental smoking	42/105 (40)	14/37 (37.9)	18	0.99 (0.42–2.00)	—
Bedrooms in residence[1]	3.5 (3.1 ± 0.81)	3.5 (3.1 ± 0.96)	23	1.05 (0.64–1.61)	—
Members of household[1]	4.0 (4.1 ± 1.32)	4.5 (3.9 ± 1.23)	14	0.86 (0.64–1.15)	—
Preadmission Ibuprofen usage	55/119 (46.2)	32/39 (82)	2	6.36 (2.36–15.00)	1.94 (0.80–3.18)

OR, odds ratio; IMD, index of multiple deprivation.
[1]Values are expressed as median (mean ± standard deviation).
[2]Twenty mixed viral–bacterial infections were excluded from analysis and together with unknown a etiology added to the missing data.

that caused by group A streptococcal infection.[20,21] Several explanations have been suggested for these findings, ranging from a simple association to more complex pathophysiological hypotheses.

It seems plausible that perhaps the increased Ibuprofen risk may simply reflect the fact that these patients were unwell, had a higher fever and in more discomfort thus were more likely to need antipyretics or analgesics and therefore increasing the odds of receiving Ibuprofen. However, recent fever may play an important regulatory role in the control of infection and Ibuprofen usage in this context may be immunomodulatory. Many pneumococcal serotypes are temperature-sensitive, with thermal death points between 40 and 41°C.[22,23] The presence of fever enhances immunological responses resulting in the reduction of replication of viruses and bacteria and effective suppression of fever may interfere with these responses.[24] This is suggested clinically by Prymula et al.[25] who compared fever, local pain responses, and post-vaccination specific-antibody levels between children given PCV10 and randomized into two groups of either Paracetamol prophylaxis for the first 24 hr or not. Fever >38°C was less common in the prophylactic group after both the primary and booster vaccinations, with associated significantly lower pneumococcal antibody responses.[25]

It was surprising that parental smoking was not a risk factor for empyema/severe complicated pneumonia, given that there was a relative excess of smoking in the studied cohort (40%) compared to the national average rate of 21% for adults.[26] Pooled review data showed that household smoking is a significant risk factor of lower respiratory tract infections and asthma in children.[27–29] Self-reporting of parental smoking is usually underestimated.[30,31] As the present study collected information on parental smoking based on self-reporting this may have biased the analysis of smoking as a predictor of empyema. It has been suggested that measuring cotinine levels in blood and urine of children could overcome under reporting of passive smoking.[30,31] Similarly, self or parental reporting of asthma may be compromised due to the variability of defining asthma in children.[32,33]

Strengths and Limitations

The strengths of this study include the prospective design evaluating the risk factors for development of empyema in a defined cohort with radiologically classified pneumonia using robust diagnostic etiological investigations.[8] It is limited by the fact that association of the significantly identified risk factors does not imply causal relationship. Therefore the interpretation of these findings should be guarded. Further limitation is that no details on the frequency and doses of Ibuprofen and timing of its use in relation to the start of the illness. This information was deemed difficult to ascertain because of over the counter self-prescription.

Another limitation is the risk of circularity because of the methods of pathogen detection. Rates of specific pathogen detection are low in children with pneumonia and in our cohort molecular testing of pleural fluid provided a definitive diagnosis of bacterial infection in a high proportion. This may reflect the fact that these children were genuinely at higher risk because of bacterial infection but may be a reflection of ascertainment bias. Our interpretation is that this is a genuine increased risk but without adopting alternative diagnostic methods into routine practice for children with pneumonia it is impossible to be certain.

In conclusion, pre-hospital administration of Ibuprofen, and confirmed bacterial infection were associated with increased risk of empyema during hospital admission of children with pneumonia. We suggest a large-scale population-based study involving both primary and secondary care settings would help to investigate the role of Ibuprofen use in modulating the course of disease in children with pneumonia.

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